CARDIAC POWER OUTPUT, ITS ROLE IN DEFINING HEART FAILURE FOR FUTURE MECHANICAL CIRCULATORY SUPPORT

By

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ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
ACEI	Angiotension Converting Enzyme Inhibitor
ARB	Angiotension Receptor Blocker
BSA	Body Surface Area
HF	Heart Failure
CI	Cardiac Index
CO	Cardiac Output
CPI	Cardiac Power Index
CPO	Cardiac Power Output
CMS	Centers for Medicare and Medicaid Services
CVP	Central Venous Pressure
EF	Ejection Fraction
ICU	Intensive Care Unit
LVSWI	Left Ventricle Stroke Work Index
MAP	Mean Arterial Pressure
MCS	Mechanical Circulatory Support
MVO2	Myocardial Oxygen Consumption
PCWP	Pulmonary Capillary Wedge Pressure
NYHA	New York Heart Association
SVR	Systemic Vascular Resistance

ABSTRACT

Cardiac Power Output (CPO) has shown to effectively indentify declining cardiac performance in Heart Failure (HF) patients. We compared CPO to other commonly used hemodynamic parameters to establish its usefulness in determining when Mechanical Circulatory Support (MCS) is required. A retrospective study of 28 HF patients previously implanted with MCS were analyzed at 3 stages of pharmacological support. Studied subjects were separated into two categories (survived versus deceased) to compare contractile reserve differences in order to predict when complete cardiac dysfunction was met. CPO and Cardiac Power Index (CPI) were the two hemodynamic parameters that identified remaining contractile reserve in the declining heart ($p < 0.05$). Other commonly used hemodynamic parameters failed to provide information that can detect the need for MCS. Patients who decreased below 0.70 (Watts) had higher incidences of mortality and /or morbidity. Clinicians who cannot medically manage HF patients above 0.70 W may consider MCS as an alternative treatment to retain hemodynamic stability.

INTRODUCTION

With Heart Failure (HF) at the forefront as the fastest growing type of heart disease, searching for a hemodynamic parameter to predict HF severity and when additional support is required can provide clinicians the information necessary to correctly manage these patients. As the heart progressively declines, its pumping capability cannot produce the contractile energy the arterial system requires to support circulation(1). At this point clinicians intervene with pharmacological agents to increase cardiac function and reduce HF symptoms. As HF progresses and patients become non-responsive to medical management, a hemodynamic formula “Cardiac Power Output” (CPO) can provide clinicians with an accurate representation of declining heart function. CPO as a hemodynamic parameter has been proven to be a useful tool in determining cardiac reserve and HF severity (1-7). The four determinants that regulate cardiac performance are heart rate, stroke volume, aortic pressure, and contractility. The interrelationship of pressure, resistance, and flow are what make up the three parameters of hemodynamics. What separates CPO from other hemodynamic parameters is that it integrates all of these values to generate the hydraulic energy the heart produces as it pumps.

Current HF treatments consist of administering positive inotropes to assist with increasing cardiac contractility. Although various forms of treatments exist to re-stimulate the declining heart, with time pharmacological interventions reach a point where they no longer are efficacious. There is an insufficient understanding as to “when” heart function declines and becomes inadequate enough to support itself and vital organs.

A myriad of diagnostic tests exist to determine heart function, but these tests lack a concise marker that defines when further intervention is required to support the failing heart. The present study retrospectively analyzes prior MCS patient's hemodynamic values to determine which hemodynamic parameter, if any, provided signs of a regressing "reserve" and whether this could have predicted survival outcomes. Our goal was to determine the most opportune time to implant MCS devices in order to decrease the morbidity and mortality rate in this growing number of patients.

METHODS

STUDY POPULATION

28 patients (24 Male and 4 Female) with a history of HF were referred to Tucson's University Medical Center for MCS. Patients were admitted due to increased HF symptoms or were transferred from outside institutions. The studied population consisted of New York Heart Association (NYHA) Class III / IV and American College of Cardiology – American Heart Association (ACC-AHA) Stage C / D HF patients. Patient's pre-implant data were taken over the interval of July 2008 to April 2011 (Table 1). Approval for human data review was granted by the University Medical Center, Tucson and the Institutional Committee on Human Research.

Table 1: Baseline Patient Demographics (No Inotropic Treatment)

Heart Failure Patients (n= 28)	**Values**
Age	53 ± 13
BSA	2.0 ± 0.2
HF Etiology	
Ischemic	13 (46%)
Non-Ischemic	15 (54%))
ICD	19 (68%)
HR	81 ± 18 BPM
MAP	82 ± 11 mmHg
SVR	1724 ± 483 mmHg
CVP	21 ± 7 mmHg
Mean PCWP	29 ± 4 mmHg
LVSWI	15 ± 5 g/m2/beat
EF	22 ± 9 %
Cardiac Output	3.14 ± 0.72 L/min
Cardiac Index	1.61 ± 0.39 L/min/m2
Cardiac Power Output	0.57 ± 0.13 W
Cardiac Power Index	0.29 ± 0.06 W/m2
Creatinine	1.65 ± 0.52 mg/dL
GFR	37 ±8 mL/min

**BSA, Body Surface Area; HF, Heart Failure; ICD, Implantable Cardioverter Defibrillator; HR, Heart Rate; MAP, Mean Arterial Pressure; SVR, Systemic Vascular Resistance; CVP, Central Venous Pressure; PCWP, Pulmonary Capillary Wedge pressure; EF, Ejection Fraction; GFR, Glomerular Filtration Rate*

DATA COLLECTION

Patient data was collected at three stages of medical management to measure remaining contractile reserve in the studied population. Hemodynamic information was initially gathered at baseline (no inotropic treatment), which consisted of subjects on standard HF medications, ß-blocker, diuretics, ACE inhibitors, and ARBs. The second stage (Initial Inotropic Treatment) was the initiation of dobutamine, milrinone, or dopamine to increase cardiac contractility for hemodynamic stability. The third stage (Peak Inotropic Treatment) was considered the highest inotropic dose or change of inotropic agent(s) before patients became non-responsive and in need of MCS.

Hemodynamic data was collected in three ways, right heart catheterization, Swan-Ganz catheter, or during an echocardiography exam. The baseline (No Inotropic Treatment) information was gathered when patients were first admitted into the intensive care unit (ICU) while on standard HF medications. As HF symptoms progressed and patients were placed on inotropic support, inotropic doses and type were documented within four hours of administration and considered the Initial Inotropic Treatment (Table 2). Throughout the patients' admission, medical management was adjusted based on hemodynamic requirements and/or tolerance. The hemodynamic value reported as Peak Inotropic Treatment was the highest inotropic support the patient received or if the agent itself was changed due to tolerance prior to MCS implantation. Table 2 displays documented mean inotropic doses while in the ICU setting. Patients were administered one or multiple variations of inotropic treatments to sustain physiological homeostasis.

Table 2 Administered Inotrope Doses

Positive Inotrope	Initial Treatment (mcg/kg/min)	Peak Treatment (mcg/kg/min)	P-value
Dobutamine	4.7	6.0	> 0.05
Milrinone	0.47	3.23	> 0.05
Dopamine	4.5	3.78	> 0.05

**Inotropic support were averaged as mean dosages for the two treatment stages*

Hemodynamic differences between patients who survived versus those who died were separated into two categories. Patients considered in the "survived" category were patients who survived 90 days from implant date. The "deceased" group were patients who died within 90 days of receiving a MCS device. Nine hemodynamic parameters were used to assess remaining "cardiac contractile reserve" in the declining HF patients:

- Cardiac Output - L/min, (HR x SV)
- Cardiac Index - L/min/m^2, (CO/BSA)
- Ejection Fraction %, [(SV/EDV) x 100]
- LVSWI - g/m2/beat, [SVI x (MAP - mean PCWP) x 0.0136]
- Mean Arterial Pressure - mmHg, [Systolic + (2 x diastolic)] / 3
- Systemic Vascular Resistance – dynes/cm^3/mmHg, [(MAP-CVP)/CO x 80]
- Cardiac Power Output - Watts, [(MAP x CO) x 0.0022]
- Cardiac Power Index - W/m^2, (CPO/BSA)

The above hemodynamic values were compared at the three stages of pharmacological therapy to identify whether any relative differences existed within each of the hemodynamic parameters. This permitted the identification of hemodynamic parameters

characterizing the remaining cardiac contractile reserve and whether any of these variables might predict survival outcomes once patients regress into severe stages of HF.

STATISTICS

Statistical analysis was done using Data Analysis and Statistical Software Stata 11 (StataCorp LP, TX, USA). An independent two sample t-test with unequal variance was used to identify whether cardiac contractile reserve still existed in one or both of the studied groups. Hemodynamic values were tested to determine which hemodynamic parameter gave the better representation of remaining contractile reserve. All data are presented as mean ± SD.

RESULTS

Of the 28 HF patients studied, 21 survived and 7 died within 90 days of receiving an implanted device. Six of the seven patients who died, died from end organ failure (brain, liver, and kidney). The 21 patients who survived 90 days post implant 16 had a left ventricular assist device (HeartMate II) as an end of life care support (destination therapy) or until an orthotopic heart became available to transplant (bridge to transplant). The remaining 5 survivors had the Syncardia temporary Total Artificial Heart (TAH-t) as a temporary support device for bridge to transplant. Of the surviving 21 patients, one died within six months of receiving MCS from systemic inflammatory response syndrome.

BASELINE HEMODYNAMICS

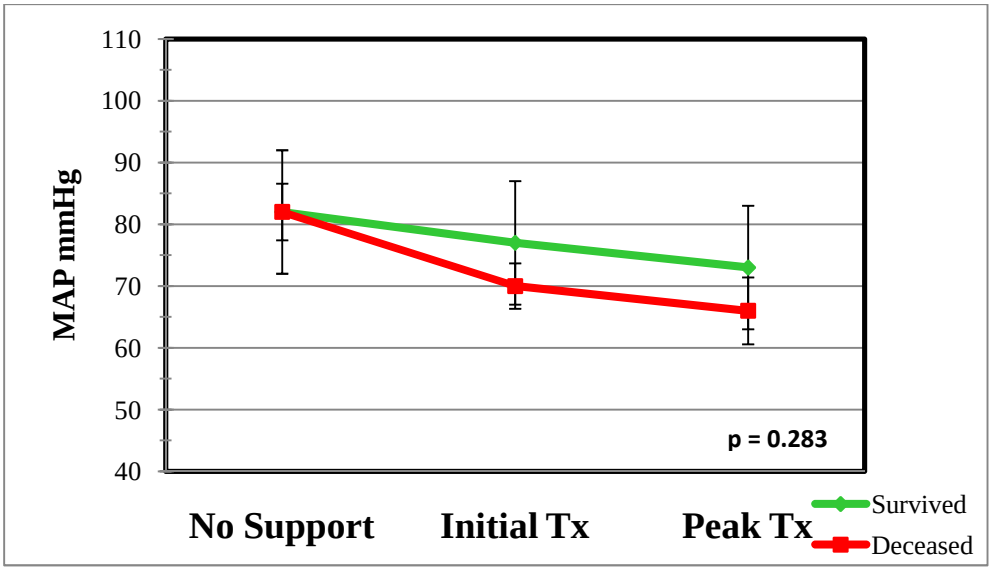
All of the hemodynamic values as shown in Table 1 are abnormal values with the exception of heart rate and mean arterial pressure. Baseline values were recorded when the patients were receiving standard HF medications (ß-blocker, diuretics, & ACEI/ARB). The other hemodynamic parameters (Mean Arterial Pressure, Cardiac Output, Cardiac Index, Ejection Fraction, Left Work Stroke Work Index, Systemic Vascular Resistance, Cardiac Power Output, and Cardiac Index) were all below healthy adult ranges.

MEAN ARTERIAL PRESSURE

Mean arterial pressure is the easiest way to assess hemodynamic stability in patients. All that is required is a blood pressure cuff, and measures systolic and diastolic pressures. MAP (systolic + (2 x diastolic) / 3) is the parameter that becomes the first tell-tale in identifying hemodynamic abnormalities. With MAP being the most commonly

used parameter to assess systemic homeostasis, we attempted to analyze whether MAP can detect contractile reserve as inotropic support is administered at different stages. The studied group presented with initial MAP of 82 ± 11 mmHg while medically managed with standard HF medications (Table 1). Although MAP was slightly below normal, it was not the contributing factor for hemodynamic instability when admitted into ICU. MAP is a variable that can be manipulated to a desired range with the administration of norepinephrine and/or epinephrine to increase systemic vascular resistance. When initial inotropic support was administered, MAP steadily declined in both the survived and deceased group (Figure 1). As inotropic support increased (Peak Inotropic Treatment), MAP continued to decline but there were no significant differences between the two groups (p = 0.283).

Figure 1: Mean Arterial Pressure

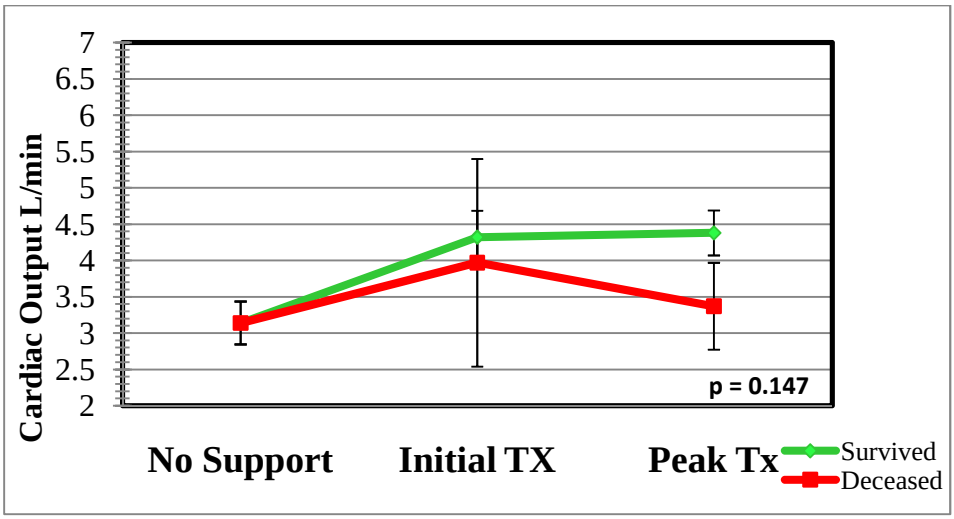


*p-value > 0.05 when survived versus deceased were compared

CARDIAC OUTPUT

During standard medical management, the baseline mean cardiac output for this group of patients was well below the average healthy resting range at 3.14 ± 0.72 L/min, thus the need for further inotropic support. With the initial dose of positive inotropic agent, cardiac output increased in both groups. With initial inotropic administration, the survived group reached a cardiac output of 4.32 ±1.5 L/min, while the deceased group reached 3.97 ± 2.5 L/min. With peak inotropic treatment, the survived and deceased groups parted in two separate directions with cardiac output having plateaued at 4.38 ± 1.4 L/min as the deceased group declined to 3.37 ± 1.47 L/min. With the initial treatment of inotrope, cardiac output increased in both groups, but as the peak dosages were administered, the heart no longer became capable of increasing its cardiac output. When the survived and deceased groups were compared at this peak dose, there was no statistical significance between the two groups (p = 0.147).

Figure 2: Cardiac Output

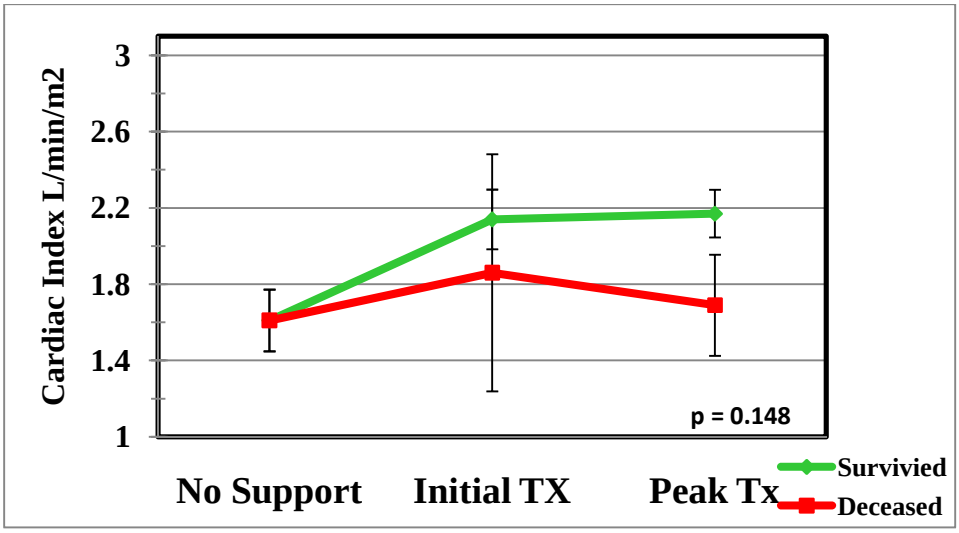


*p-value > 0.05 when survived versus deceased were compared

CARDIAC INDEX

Measuring cardiac output and the distribution of volume over body surface area has shown to be a good measurement of organ perfusion. As in Figure 1, the studied patients presented with lower than normal hemodynamic values with a decreased cardiac index of 1.61 ± 0.39 L/min/m2 relative to the average healthy adult (2.5 – 4.0 L/min/m2). In the survived group, cardiac index increased to 2.14 ± 0.62 L/min/m2, but remained constant while on peak treatment at 2.17 ± 0.65 L/min/m2. The deceased group displayed slight rise in index during the initial treatment, but regressed back to baseline (1.69 ± 0.65 L/min/m2) while on peak inotropic support. In Figure 3, cardiac index was not a useful hemodynamic marker to identify if contractile reserve remained or whether it was able to predict survival outcomes between the survived and deceased group (p = 0.148).

Figure 3: Cardiac Index

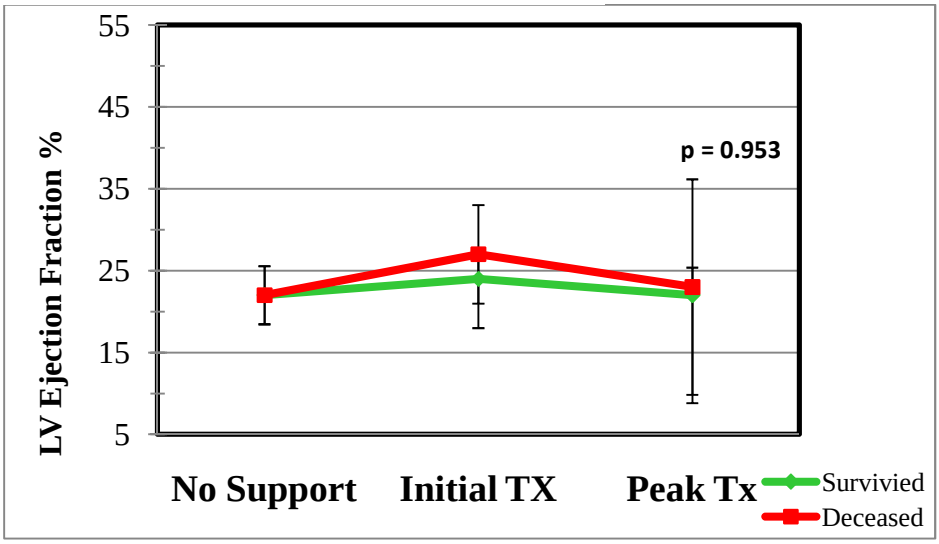


*p-value > 0.05 when survived versus deceased were compared

LEFT VENTRICLE EJECTION FRACTION

Ejection fraction data (Figure 4) from echocardiography was found not to be useful in detecting functional cardiac reserve in the survived or deceased group (p = 0.953). When placed on initial inotropic treatment, both groups responded similarly and followed a similar trend during peak inotropic support (22 ± 9.5% vs. 23 ± 22.8%). There was a large standard error for the deceased group due to a select few having systolic HF with preserved EF.

Figure 4: Ejection Fraction



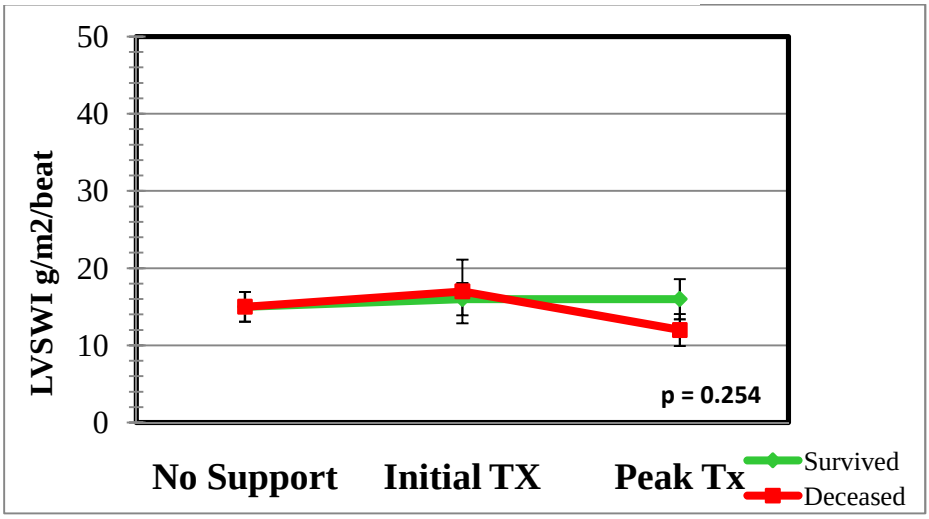
*p-value > 0.05 when survived versus deceased were compared

LEFT VENTRICLE STROKE WORK INDEX

The mean left ventricle stroke work index for the average healthy adult ranges between 50 – 62 g/m2/beat. The studied patients were all well below the healthy range despite being managed with standard HF medication. Both the survived and deceased groups presented with a LVSWI of 15 ± 5 g/m2/beat, but once placed on initial inotropic

support, both groups made minimal improvements in LVSWI (Figure 5). When additional medical support was supplied, the survived and deceased groups reaped no beneficial effects (p = 0.254), leaving LVSWI as an unreliable hemodynamic indicator to detect cardiac reserve or determine whether the remaining reserve is indicative of survival post device implant.

Figure 5: Left Ventricular Stroke Work Index



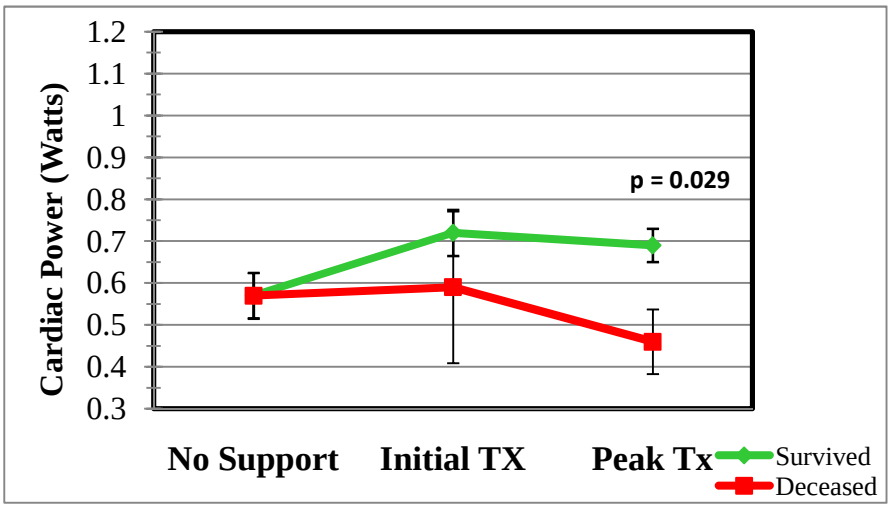
*p-value > 0.05 when survived versus deceased were compared

CARDIAC POWER OUTPUT

Baseline cardiac power output as in the other hemodynamic values was low in comparison to normal healthy resting values. Baseline CPO characteristics while treated with standard HF medication were 0.57 ± 0.13 Watts (W) in both groups (Figure 6). With initial inotropic treatment stage, CPO increased in the survived group but statistically there was no difference when compared to the deceased group. Inotropic support continued with increased dosages or additional agents, CPO in the survived group plateaued and the value in the deceased group declined. As the data shown in Figure 6,

CPO remained constant initially but while on peak inotropic support, the CPO calculation was able to identify the existence of contractile reserve for the survived group but not for the deceased group (0.69 ± .039 W vs. 0.46± .077 W). Statistical comparison between the two groups identified CPO as having statistical significance (p = 0.029) and the hemodynamic parameter that was able to differentiate the remaining reserve between HF patients who survived and died post MCS.

Figure 6: Cardiac Power Output



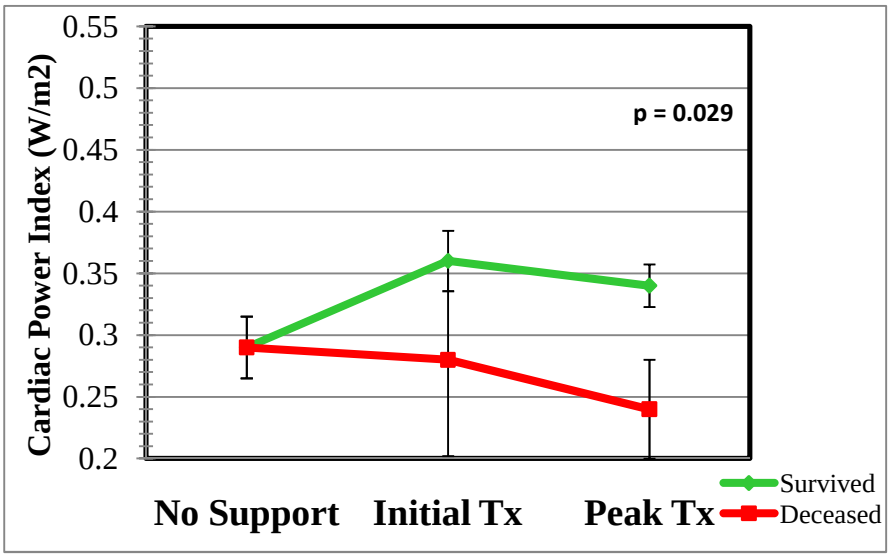
*p-value < 0.05 when survived versus deceased were compared

CARDIAC POWER INDEX

In addition, Cardiac Power Index (CPI), a byproduct of CPO as a measure of body surface area (BSA), was tested to determine if additional information can be gathered by assessing the contractile energy the heart generates to fulfill the systemic circuit after every cardiac cycle. During the initial inotropic treatment, CPI increased in the survived group as it did in CPO but slightly decreased as dosages were increased or altered to other agents. The peak differences in the survived versus the deceased group provided

statistical significance when contractile reserves were compared between the two groups ($p = 0.038$). In Figure 7, CPI revealed if contractile reserve decreases below 0.34 W/m^2, the likelihood of sustaining hemodynamic instability increases and so does the rate of mortality.

Figure 7: Cardiac Power Index



*p-value < 0.05 when survived versus deceased were compared

DISCUSSION

The current selection criteria for MCS is governed by The Centers of Medicare and Medicaid Services (8). For patients who have been medically managed with positive inotropic support and no longer respond favorably, MCS is seen as the next viable step of treatment. Patient selection is one of the key components to ensuring patients have successful outcomes not only for MCS, but also heart transplantation. The current CMS guidelines use left ventricular EF and Myocardial Oxygen Consumption ($MVO_{2)}$ tests as criteria to assess cardiac and systemic status for possible MCS. In the present study, as Marmor et al. reveals (9), EF did not display any differences between subjects during peak inotropic stimulation. In addition, results from prior MVO2 studies on patients in latter stages of HF have shown to be of inconclusive value when peak cardiac function was measured (4;10;11). Patients with NYHA Class III / IV symptoms are known to be severely compromised when tested physically due to progressive muscle deconditioning, poor vascular circulation, compromised lung capacity, and anemia. Although EF and MVO2 examinations have their respective roles in measuring specific parameters of heart function, they do not provide reliable indicators of cardiac function in these severely compromised HF patients.

Right and/or left heart catheterizations provide very useful information in gathering pressure and volume changes in specific areas of the heart. The limiting factors to assess cardiac function in this manner are that patients are placed in a supine position with hemodynamic measurements taken without stimulating peak cardiac contractility. Measuring heart function in this manner does not provide any information on the reserve

potential. Being able to determine contractile reserve is essential to knowing how much "pump" is still left in the heart and whether it has fully maximized its reserve means. Resting values alone do not provide a sufficient amount of useful information on cardiac capacity in healthy versus diseased hearts, however stimulation to achieve peak contractile ability is when diseased hearts becomes apparent from healthy ones.

With the limited physical and physiological abilities of this population of HF patients, a method that has proven to be an effective way to assess peak contraction is by using positive inotropes to stimulate a response. Using inotropic agents to generate peak contractile force has proven to stimulate the heart in the same manner as a response to exercise (9;12). In severely compromised patients, this response to inotropes may be the only viable option to determine how much contractile energy still remains. The current study provided information on initial inotropic support and its ability to stimulate remaining contractile reserve. Overtime, although inotropic support is increased or altered, therapeutic saturation was met, indicative of the heart having already reached its maximum ability to generate a "pump".

In the present study CPO and CPI were the only hemodynamic parameters that distinguished cardiac contractile reserve and the threshold survived patients attained in order to have successful outcomes, post device implantation. Although invasive inotropic stimulation may not be the first choice to assess cardiac contractile reserve, in some patients, assessing peak CPO and/or CPI invasively provides information on whether pharmacological support is still sustaining its efficacy and if any contractile reserve still remains.

Non-invasive methods to measure CPO and CPI have been used over five years and have been found to effectively determine the severity of HF (2-5;10;13;14). With proven non-invasive equipment such as the Innocor re-breathing system (Copenhagen, Denmark), it can detect the severity of HF by using an oxygen enriched soluble gas (0.5% nitrous oxide) with an insoluble gas (0.1% sulfur hexafluoride) to measure CPO. This then can become a convenient way to monitor patients in earlier stages of HF. This will allow physicians to effectively decide when to intervene with pharmacological support or when additional MCS is required.

In conclusion, estimating CO and MAP either invasively or non-invasively in addition to using the CPO formula, may provide clinicians with an additional prognostic marker to determine the hearts peak contractile reserve. Peak CPO values may also assist clinicians with determining future therapeutic treatments including timely MCS. CPO calculation identifies the existence contractile reserve in some hearts and this may assist in decisions concerning MCS. In patients categorized in NYHA Class III / IV or ACC-AHA Stage C / D heart failure, if a peak CPO greater than 0.70 W cannot be attained intrinsically or pharmacologically, these patients are prime candidates for using MCS. Patients with CPO of 0.70 W have an increased incidence of mortality and/or morbidity.

DISCLOSURE

No financial funding was provided for the following study.

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